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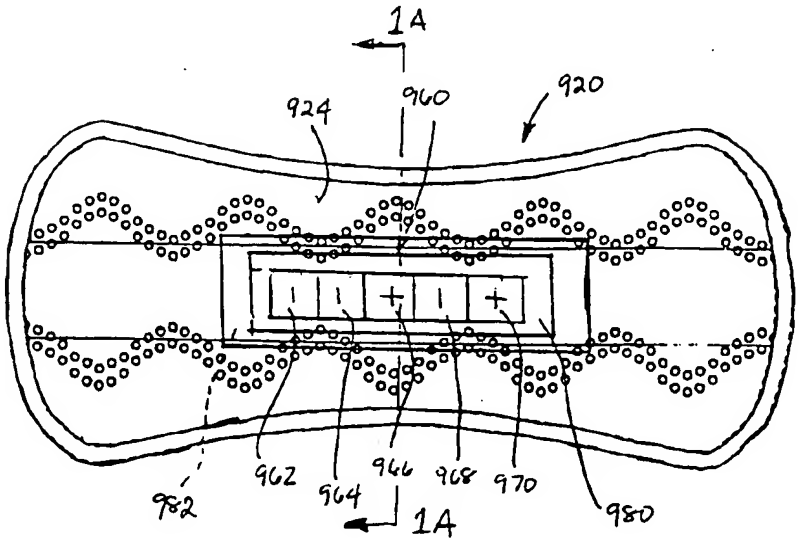

(57) Abstract

A multiple diagnostic device for a woman's health is provided comprising a biosensor being able to detect multiple target analytes in a women's bodily fluids and on or through the skin, wherein the analytes are germane to a women's health. The bodily fluids consist of vaginal secretions, menses, blood, urine and saliva. Preferably, the biosensor comprises at least one bio–recognition element for use in detecting multiple one biological analytes. The multiple diagnostic device may be used in one or more conventional absorbent articles.

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MULTIPLE DIAGNOSTIC DEVICE FOR A WOMAN'S HEALTH

FIELD OF THE INVENTION

The present invention relates to a multiple diagnostic device which detects two or more types of hormones related to a woman's menstrual cycle, ovulation, pre-menstrual syndrome and pregnancy. Also, the multiple diagnostic device may be placed within or in a conventional type of feminine protection absorbent article and an incontinent absorbent article. The multiple diagnostic device may also be used to detect one or more types of bacteria, virus and other known disease indicators.

BACKGROUND OF THE INVENTION

Today, disposable articles, such as absorbent articles, adult incontinence briefs, sanitary napkins and tampons, are widely used in infant and toddler care and in the care of incontinent or menstruating adults as a means of containing, isolating and disposing of bodily wastes. These articles have generally replaced reusable, washable cloth garments as the preferred means for these applications because of their convenience and reliability. The disposable articles respond to a defecation, urination or discharge event by absorbing or containing bodily wastes deposited on the article. Some disposable articles also signal a defecation, urination or discharge event after it has occurred (e.g., wetness indicators, temperature change detection). Other disposable absorbent articles known in the art comprise a chemically reactive means to detect various substances in the wearer's waste(s). However, none of these specifically detect target potentially pathogenic microorganisms such as bacteria, viruses, fungi, and parasites (e.g., protozoans) and/or related biomolecules, all of which require a high degree of selectivity (i.e., specificity) and sensitivity versus purely chemical agents. Additionally, the articles do not predict when a health-related event is about to occur and signal wearer or caregiver that prophylactic or remedial action is required prior to the onset of clinically observable symptoms.

SUMMARY OF THE INVENTION

Accordingly, the invention provides a multiple diagnostic device for a woman's health comprising a biosensor being able to detect multiple target analytes in a woman's bodily fluids and on or through the skin, wherein the analytes are germane to a women's health. The bodily fluids consist of vaginal secretions, menses, blood, urine and saliva. Preferably, the biosensor comprises at least one bio-recognition element for use in detecting multiple biological analytes.

As previously stated, biological analytes tested are germane to a woman's health indicating at least one of the following including 1) the onset of menstruation, 2) the presence of ovulation, 3) the presence of a sexually transmitted disease, 4) the state of pregnancy, 5) the presence of infection, 6) the presence of hormone fluctuations, 7) ovarian reserve, 8) the presence of menopause, 9) the presence of osteoporosis, 10) the presence of an iron deficiency, 11) electrolyte balance, 12) nutritional status, 13) stress level and 14) combinations thereof.

Also preferably, an absorbent article may comprise the multiple diagnostic device of the present invention. The absorbent article is a conventional one known in the art having a topsheet, a backsheet joined to the topsheet, and an absorbent core positioned between the topsheet and the backsheet. The topsheet has a top surface facing a user and a bottom surface facing away from a user. The multiple diagnostic device may be positioned on the top surface of the topsheet. The multiple diagnostic device may be positioned between the topsheet and the backsheet of the absorbent article. Preferably, the multiple diagnostic device will be positioned adjacent to the bottom surface of the topsheet and above the absorbent core. The multiple diagnostic device may also be placed within the absorbent core of the absorbent article.

Ideal absorbent articles for the invention herein include one selected from the group consisting of a sanitary napkin, an interlabial device, a tampon, a patch, a liquid collection device, an incontinent device and combinations thereof.

BRIEF DESCRIPTIONS OF THE DRAWINGS

While the specification concludes with claims particularly pointing out and distinctly claiming the subject matter which is regarded as forming the present invention, it is believed that the invention will be better understood from the following descriptions which are taken in conjunction with the accompanying drawings in which like designations are used to designate substantially identical elements, and in which:

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "sanitary napkin" or "napkin" refers to an absorbent article which is worn by females adjacent to the pudendal region, generally external to the urogenital region, and which is intended to absorb and contain menstrual fluids and other vaginal discharges from the wearer's body (e.g., blood, menses, and urine). As used herein, the term "pudendal" refers to the externally visible female genitalia. It should be understood, however, that the present invention is also applicable to other feminine hygiene or catamenial pads such as pantiliners, or other absorbent articles such as incontinence pads, and the like. By the term "zone of menses insult" it is meant herein that area on the sanitary napkin most likely to consistently receive a menses discharge from a female wearer.

Non-limiting examples of panty liners and sanitary napkins which may be provided with a diagnostic device include those manufactured by The Procter & Gamble Company of Cincinnati, Ohio as: ALWAYS® Pantiliners with DriWeave® manufactured according to U.S. Patent Nos. 4,324,246; 4,463,045; and 6,004,893; ALWAYS® Ultrathin Slender Maxi with Wings manufactured according to U.S. Patent Nos. 4,342,314, 4,463,045, 4,556,146, B1 4,589,876, 4,687,478, 4,950,264, 5,009,653, 5,267,992, and Re. 32,649; ALWAYS® Regular Maxi; ALWAYS® Ultra Maxi with Wings; ALWAYS® Maxi with Wings; ALWAYS® Ultra Long Maxi with Wings; ALWAYS® Long Super Maxi with Wings; and ALWAYS® Overnight Maxi with

Wings. An example of a panty liner with a diagnostic device is shown in Figs. 1 and 1A. An example of a sanitary napkin with a diagnostic device is shown in Fig. 2.

Non-limiting examples of tampons which may be provided with a diagnostic device, and applicators therefor, are described in U.S. Patent Nos. 4,726,805; 4,846,802; 4,960,417; 5,087,239; 5,279,541; 5,346,468; 5,348,534; 5,531,674; and 5,566,435. In addition, the diagnostic device could also be placed on a digitally insertable tampon. An example of a tampon with a diagnostic device is shown in Fig. 5.

The cyclic nature of the hormones of the menstrual cycle (i.e., the full 28 day cycle) make them useful in understanding fertility and, in general, the position of an individual during her cycle. This goes beyond current uses of hormones to predict ovulation and pregnancy. For example, progesterone peaks and then drops just prior to menstruation. Estrogen also declines just prior to menstruation. Thus, in combination, assay for these two hormones will allow reliable prediction of the onset and the presence of menstruation. The timing of the peak of these hormones, along with their subsequent drop, may allow an almost daily marking of the time before menstruation.

Similar examples may be developed for other points of interest in the cycle. Follicle Stimulating Hormone (FSH) exhibits a peak about one week prior to ovulation, giving more advance timing for pregnancy planning than assays for the luteinizing hormone, which exhibits a sharp peak at the time of ovulation. Two to three days of fertility may be missed when relying only on assay of the luteinizing hormone. Thus, in a diagnostic for ovulation herein, it is highly preferred to measure for both the Follicle Stimulating Hormone and the luteinizing hormone along with estrogen.

A rise in Follicle Stimulating Hormone to a near constant amount signals the approach of menopause. This may be of use in planning healthy approaches to menopause, such as Hormone Replacement Therapy, nutritional changes, and checks for osteoporosis.

Thus, a diagnostic testing for multiple hormones presents a much broader and more useful information set to a woman than single tests of individual cycle information proposed by the prior art. Technologies which allow multiple analyte assays are thus of potential use in this invention proposed by the prior art. These include, but are not limited to, antibody labeled microbeads, Silas ™ surface analysis, or membrane based biosensors.

SILAS™ or SILICON Assay Surface Technology is a proven method for the detection of specific target molecules. This thin film based technology has successfully been used for the development of diagnostic tests to detect bacterial and viral antigens from Group A Streptococcus, Group B Streptococcus, Chlamydia, and Influenza A and B (Optical Immunoassay (OIA®)).

The wafer consists of a silicon support with an optical coating and attachment layer. This wafer surface technology enables the direct visual detection of a physical change in the optical thickness of molecular thin films. This change in thickness is due to the specific capture of an analyte on the surface. When a substrate is added, this binding event is amplified and again increases the surface thickness of the molecular thin film. This change in thickness alters the reflected light path and is visually perceived as a color change. Slight changes in optical thickness produce a distinct visible color change. A positive result appears as a purple spot on the predominant gold background. When a target is not present in the sample, no binding takes place. Therefore, the optical thickness remains unchanged and the surface retains the original gold color indicating a negative result.

Thus, in a first aspect, the invention features a device for detecting the amount or presence of an analyte of interest. The device includes a substrate which has an optically active surface exhibiting a first color in response to light impinging thereon. This first color is defined as a spectral distribution of the emanating light. The substrate also exhibits a second color which is different from the first color (by having combination of wavelengths of light which differ from that combination present in the first color, or having a different spectral distribution, or by having an intensity of one or more of those

wavelengths different from those present in the first color). The second color is exhibited in response to the same light when the analyte is present on the surface.

An "optically active surface" is a surface that participates in the generation of an optical effect such that the light impinging upon that surface is in some way altered. Such optically active surfaces may be adapted to respond not only to polychromatic light (e.g., white light) but also to mono-chromatic light (e.g., laser light, which may be inherently polarized). Devices of this invention preferably produce a color signal that strongly contrasts the background interference color of the unreacted test surface and a reacted surface.

Specifically, the invention features similar devices in which the substrate has an attachment layer formed from a chemical selected from the group consisting of dendrimers, star polymers, molecular self-assembling polymers, polymeric siloxanes, and film forming latexes; the substrate itself is formed from a material selected from the group consisting of monocrystalline silicon, a amorphous silicon on glass, amorphous silicon on plastic, a ceramic, polycrystalline silicon, and composites of these materials; and the substrate may have an optical thin film formed from a material selected from the group consisting of silicon nitride, silicon/silicon dioxide composites, titanates, diamond, oxides of zirconium, and silicon carbide.

The substrate is selected from the group consisting of glass, and plastic, comprising a layer of amorphous silicon on its surface, whereby an optically active surface is produced; the optically active surface includes monocrystalline silicon or metal; the substrate in metal further having a layer of amorphous silicon; a receptor layer receptive to an analyte is provided with a specific binding partner for the analyte; the receptor layer is formed from material selected from the group consisting of antigens, antibodies, oligonucleotides, chelators, enzymes, bacteria, bacterial pili, bacterial flagellar materials, nucleic acids, polysaccharides, lipids, proteins, carbohydrates, metals, viruses, hormones, and receptors for said materials; and the first color is golden in appearance and the second color is purple or blue in appearance to the eye.

In another related aspect, the invention features a method for detecting an analyte of interest in a sample, by the steps of providing a thin film optical immunoassay device having a substrate, having an upper and a lower surface, and supporting on its upper surface, an unlabeled antibody layer bound to the substrate, at least one layer containing the analyte from the sample, the analyte containing layer supporting at least one layer having an enzyme conjugate complex with the analyte; contacting the enzyme conjugate with a precipitating agent; incubating for a time period sufficient to cause precipitation of product from interaction of the precipitating agent and the enzyme; and optically measuring the mass change of the enzyme conjugate layer and the unlabeled antibody layer as an indication of the amount of the analyte in the test sample.

Preferably, the enzyme conjugate has an immobilized peroxidase or an anti-bacterial anti-body-horseradish peroxidase complex; or the enzyme conjugate is alkaline phosphatase and comprises an anti-bacterial -antibody- alkaline phosphatase complex; and the precipitating agent is a substrate containing 5-bromo-4chloro-3indolyl phosphate.

In practice, an array of sensors may be placed on a surface to be brought into contact with a suitable sample. Samples include, but are not limited to urine, saliva, sweat, and vaginal discharge. Alternatively, the sensor may be placed on the skin. The individual sensors respond to their respective analytes and produce a visually detectable signal. This may be as simple as a color or refractive index change, or may involve a change in an electrical signal such as due to current flow through a biosensor membrane.

The latter type of assay lends itself to a device which may incorporate an algorithm to detect the changes in hormone levels. This may then be displayed in an easy to understand format for the user.

For example, antibodies to the appropriate hormones may be immobilized on the surface of the Silas optical wafers by methods known in the art. These wafers may then be separated and arranged in a known pattern on a detection article, for example, an absorbent article. Similarly, these antibodies could be immobilized on microbeads and arranged in a lateral flow assay device suitable for urine or saliva matrices. Again, multiple reagents are used in an array giving readout of all analytes simultaneously. Also,

other analytes may be detected in combination with hormones. These include biomarkers for other conditions of interest, such as infections, osteoporosis, etc.

Another immunoassay method comprises applying an aqueous solution containing the analyte antigen to one end of a multi-zoned test strip device such that the solution moves along the strip by capillary action. The zones are arranged so that the solution (a) first contacts and reconstitutes dry, diffusible labeled component comprising colloidal gold conjugated to an antibody specific for said analyte antigen and then (b) contacts and reconstitutes dry, diffusible biotinylated second antibody specific for the analyte antigen such that a diffusible, dispersed sandwich reaction product forms. The reaction product diffuses along the strip with the solution and into a zone containing capture component consisting of a latex and avidin complex. The avidin collects the reaction product by means of reaction with its biotin moiety. Thus, gold particles are collected and concentrated in the detection zone for visual detection.

There are also home test for LH (luteinizing hormone) and similar clinical tests for Strep A, and Chlamydia. Other sources have laboratory single-analyte tests using this chromatographic principle for human corionic gonadotropin (HCG), common infectious diseases, and DAU (drugs of abuse in urine).

Carter-Wallace's home pregnancy test, First Response®, uses plain microspheres (~1μm) coated with one antibody to hCG and very small (<50nm) red gold sol particles coated with an antibody to another hCG epitope. On mixing with a sample of urine, if the sample contains hCG, the particles are coagglutinated, thus yielding red clumps. The mixture is poured through a filter which catches the red clumps to yield a pink colored filter. With negative urine, un- coagglutinated red particles pass through the filter and no color develops on it.

Optionally, one or more of the sensors can be replaced by a sensor to detect pregnancy. In 1988 a new over-the-counter pregnancy test (Clearblue Easy™), developed and patented by Unipath, was introduced. The test uses dyed microspheres in a sandwich format to give a one step test. To prepare the test, small dark-blue dyed microspheres (○) are first coated with antibody (Ab_1) to HCG (human chorionic gonadotropin); the

microspheres (O-Ab_1) are dried on one part of a nitrocellulose strip; a second antibody (Ab_2) to HCG is immobilized on another section of the strip.

In use the strip is wetted at one end with urine. As the urine moves by capillary action, it picks up the blue microspheres (O-Ab_1), and carries them downstream; any HCG in the urine reacts with Ab_1 on the microspheres (O-Ab_1- HCG). When the flow reaches the immobilized Ab_2-1, the dyed microspheres with HCG (O-Ab_1- HCG) are captured by Ab_2-I to form a blue line caused by the HCG sandwich (O-Ab_1- HCG- Ab_2-1). The blue line signals a positive pregnancy test. Further downstream there is another line of immobilized protein (Ab_3-1) which catches unconjugated O-Ab_1.as (O-Ab_1-Ab_3-1) (independent of HCG) to form another blue line which acts as a positive procedural control. If the second line does *not* form, the test results are invalid.

The absorbent article herein (i.e., sanitary napkins, interlabial dèvices, and tampons) preferably also includes at least one multiple diagnostic device having a biosensor 60. As used herein, the term "biosensor" includes a component comprising one or more elements being adapted to detect one or more hormones, target pathogenic microorganisms or related biomolecules (e.g., an enzyme sensor, organella sensor, tissue sensor, microorganism sensor, immunosensor or electrochemical sensor), additionally having the capability to provide a signal of said detection to the wearer, caretaker, or an actuator. In certain embodiments, the elements may be biologically reactive, chemically reactive, binding, or they may operate by physical entrapment. The term "biologically reactive" is defined as having the capability to selectively interact with, and preferably bind, target pathogenic microorganisms and/or related biomolecules as described herein. The term "biologically reactive" includes, but is not limited to elements that detect the presence of enzymes. Generally, biosensors function by providing a means of specifically binding, and therefore detecting, a target biologically active analyte. In this way, the biosensor is highly selective, even when presented with a mixture of many chemical and biological entities, such as feces, menses, sweat, and saliva. Chemical sensors, on the other hand, which rely on chemically reactive means, generally do not have either the high selectivity or the amplification properties of biosensors and, therefore, are not as well suited to detect biologically reactive analytes, especially when they are present in low concentrations and/or in a complex media such as bodily fluids, bodily waste, and other

bodily discharges. Often the target biological analyte is a minor component of a complex mixture comprising a multiplicity of biological and other components. Thus, in many biosensor applications, detection of target analytes to the parts-per-billion, parts-per-trillion, or even lower levels is necessary. Accordingly, discrimination ratios of about 10^7-10^8 or greater may be required for the biosensor to recognize the target biological analyte in a complex mixture.

The biosensor of the present invention comprises a bio-recognition element, or molecular recognition element, that provides the highly specific binding or detection selectivity for a particular analyte. The bio-recognition element, or system, may be a biologically derived material such as an enzyme or sequence of enzymes; an antibody; a membrane receptor protein; DNA; an organelle, a natural or synthetic cell membrane; an intact or partial viable or nonviable bacterial, plant or animal cell; or a piece of plant or mammalian tissues, and generally functions to interact specifically with a target biological analyte. The bio-recognition element is responsible for the selective recognition of the analyte and the physico-chemical signal that provides the basis for the output signal.

Biosensors may include biocatalytic biosensors, and bioaffinity biosensors. In biocatalytic biosensor embodiments, the bio-recognition element is "biocatalytic" and may comprise an enzyme, organelle, piece of plant or mammalian tissue, or whole cells, the selective binding sites "turn over" (i.e., can be used again during the detection process), resulting in a significant amplification of the input signal. Biocatalytic sensors such as these are generally useful for real-time, continuous sensing.

Bioaffinity sensors are generally applicable to bacteria, viruses, and toxins and include chemoreceptor-based biosensors and/or immunological sensors (i.e. immunosensors). Chemoreceptors are complex biomolecular macroassemblies responsible, in part, for a viable organism's ability to sense chemicals in its environment with high selectivity. Chemoreceptor-based biosensors comprise one or more natural or synthetic chemoreceptors associated with a means to provide a signal (visual, electrical, etc.) of the presence or concentration of a target biological analyte. In certain embodiments, the chemoreceptor may be associated with an electrode (i.e., an electrical transducer) so as to provide a detectable electrical signal. Chemoreceptors may include whole or partial nerve bundles (e.g., from antennae or other sensing organs) and/or whole

or partial natural or synthetic cell membranes. On the other hand, the bio-recognition elements of immunosensors are generally antibodies. Antibodies are highly specific and can be made toward bacteria, viruses, fragments of microorganisms (e.g., bacterial cell walls, parasite eggs or portions thereof, etc.), and large biomolecules. Suitable antibodies may be monoclonal or polyclonal. In any case, bioaffinity biosensors are generally irreversible because the receptor sites of the biosensor become saturated when exposed to the target biological analyte.

In certain embodiments, biocatalytic bioaffinity biosensors may be combined, such as RNA/DNA probes or other high-affinity binding systems wherein the initial bio-recognition event is followed by biological amplification of the signal. For example, a specific bacteria may be detected by a biosensor comprising genetic material, such as DNA, as a bio-recognition element and PCR (i.e., polymerase chain reaction) amplification to detect small numbers of organisms, preferably less than or equal to about 500. Biocatalytic and bioaffinity biosensor systems are described in more detail in Journal of Chromatography, 510 (1990) 347-354 and in the Kirk-Othmer Encyclopedia of Chemical Technology, 4th ed. (1992), John Wiley & Sons, NY, the disclosure of which is incorporated by reference herein.

The biosensors of the present invention preferably detect biologically active analytes related to impending (i.e., future presentation of symptoms is likely) or current human systemic disease states, including, but not limited to, pathogenic bacteria, parasites (e.g., any stage of the life cycle, including eggs or portions thereof, cysts, or mature organisms), viruses, fungi such as *Candida albicans*, antibodies to pathogens, and/or microbially produced toxins. Additionally, the biosensor may target biologically active analytes related to impending or current localized health issues, such as stress proteins (e.g., cytokines) and IL-1α (interleukin 1-alpha) that may precede the clinical presentation of skin irritation or inflammation. In preferred embodiments, the biosensor functions as a proactive sensor, detecting and signaling the wearer or caretaker of the impending condition prior to the presentation of clinical symptoms. This allows time to administer prophylactic or remedial treatments to the wearer which can significantly reduce, if not prevent, the severity and duration of the symptoms. Further, the biosensor, by detecting

the presence of a target biological analyte in the wearer's bodily waste (e.g., menses), may detect residual contamination on a surface, such as skin, in contact with the biosensor, and provide an appropriate signal.

The physico-chemical signal generated by the bio-recognition element or elements may be communicated visually to the wearer or caretaker (i.e., via a color change visible to the human eye as in a colorimetric sensor). Other embodiments may produce optical signals, which may require other instrumentation to enhance the signal. These include flourescence, bioluminesence, total internal reflectance resonance, surface plasmon resonance, Raman methods and other laser-based methods. Exemplary surface plasmon resonance biosensors which may comprise bioconjugate surfaces as bio-recognition elements are available as IBIS I and IBIS II from XanTec Analysensysteme of Muenster, Germany. Alternatively, the signal may be processed via an associated transducer which, for example, may produce an electrical signal (e.g., current, potential, inductance, or impedance) that may be displayed (e.g., on a readout such as an LED or LCD display) or which triggers an audible or tactile (e.g., vibration) signal or which may trigger an actuator, as described herein. The signal may be qualitative (e.g., indicating the presence of the target biological analyte) or quantitative (i.e., a measurement of the amount or concentration of the target biological analyte). In such embodiments, the transducer may optionally produce an optical, thermal or acoustic signal.

In any case, the signal may also be durable (i.e., stable and readable over a length of time typically at least of the same magnitude as the usage life of the article) or transient (i.e., registering a real-time measurement). Additionally, the signal may be transmitted to a remote indicator site (e.g., via a wire, or transmitter, such as an infrared or rf transmitter) including other locations within or on the article or remote devices. Further, the biosensor, or any of its components, may be adapted to detect and/or signal only concentrations of the target biological analyte above a predefined threshold level (e.g., in cases wherein the target biological analyte is normally present in the bodily fluids, bodily waste, or other bodily discharges, or when the concentration of the analyte is below a known "danger" level).

As described above, the target analytes that the biosensors of the present invention are adapted to detect may be pathogenic microorganisms such as the pathogenic microorganisms implicated in human gastrointestinal diseases, especially those resulting in diarrhea. This type of pathogen is particularly important to monitor due to the number of children who become seriously ill or die each year from diarrheal diseases. It has been found that severe chronic diarrhea may result in weight loss and permanent physical and mental developmental retardation. A non-limiting list of pathogenic bacteria that the biosensor may detect include any of the various pathogenic strains of *Escherichia coli* (commonly known as *E. Coli*), including enteropathenogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC), enterohemorragic *E. coli* (EHEC), enteroinvasive *E. coli* (EIEC), and enteroadherent *E. coli* (EAEC) strains; *Salmonella* strains, including *S. typhi*, *S. paratyphi*, *S. enteriditis*, *S. typhimurium*, and *S. heidelberg*; *Shigella* strains such as *Shigella sonnei*, *Shigella flexneri*, *Shigella boydii*, and *Shigella dysenteriae*; *Vibrio cholerae*; *Mycobacterium tuberculosis*; *Yersinia enterocolitica*; *Aeromonas hydrophila*; *Plesiomonas shigelloides*; *Campylobacter* strains such as *C. jejuni* and *C. coli*; *Bacteroides fragilis*; and *Clostridia* strains, including *C. septicum*, *C. perfringens*, *C. botulinum*, and *C. difficile*. Non-limiting examples of commercially available biosensors adapted to detect *E. coli* are available from AndCare, Inc. of Durham, NC, as test kit #4001 and from Meridian Diagnostics, Inc. of Cincinnati, OH, as *Immuno*Card®STAT! *E. coli* 0157 Plus assay. Another non-limiting example of a commercially available biosensor adapted to detect rotavirus is available from Meridian Diagnostics, Inc. of Cincinnati, OH, as *Immuno*Card®STAT! Rotavirus assay. Another non-limiting example of a commercially available biosensor adapted to detect *Cryptosporidium* and *Giardia lamblia* is available from Meridian Diagnostics, Inc. of Cincinnati, OH, as the Merifluor Crypto/Giardia assay. Another non-limiting example of a commercially available biosensor adapted to detect *C. difficile* toxin is available from Meridian Diagnostics, Inc. of Cincinnati, OH, as the Premier *C. difficile* Toxin A assay. ABTECH, Scientific, Inc., of Yardley, PA offers "bioanalytical biotransducers", available as BB Au-1050.5-FD-X, which may be rendered biospecific (for microorganisms or other target biological analytes as described herein) by covalently immobilizing polypeptides, enzymes, antibodies, or

DNA fragments to their surfaces. Other suitable microbial biosensors, or sensing systems, for one or more of the pathogens of interest are described in U.S. Patent Nos. 5,948,694; 6,001,556; 5,106,965 (adenovirus); 5,869,272 (gram negative organisms); 5,795,717 (*Shigella*); 5,830,341; 5,795,453; 5,354,661; 5,783,399; 5,840,488; 5,827,651; 5,723,330; and 5,496,700, all of which are incorporated herein by reference.

The target analytes that the biosensors of the present invention are adapted to detect may also be viruses. These may include diarrhea-inducing viruses such as rotavirus, adenovirus (a dsDNA virus), astrovirus (an RNA virus), calcivirus (an RNA virus), and Norwalk viruses (RNA viruses), or other viruses such as rhinovirus and human immunodeficiency virus (HIV). An exemplary biosensor adapted to detect HIV is described in U.S. Patent Nos. 5,830,341 and 5,795,453, referenced above. The disclosure of each of these patents is incorporated by reference herein.

In alternative embodiments, the target analytes that the biosensors of the present invention are adapted to detect may also be parasites, especially those which inhabit the gastrointestinal tract during some point in their life-cycle (e.g., eggs or portions thereof, oocytes, trophozoites, adults). Such parasites may include protozoans, worms, and other gastrointestinal parasites. Other examples of parasites which may be detected include *Entamoeba histolytica* (which cause amoebic dysentery), *cryptosporidium*, *Giardia lamblia*, and *Dientomeba fragilis*, *Trypana cruzi* (which causes Chagas disease), and *Plasmodium falciparum*.

In yet other embodiments, the target analytes the biosensors of the present invention are adapted to detect may be fungi such as *Candida albicans*. In addition to pathogenic bacteria, certain beneficial colonic bacteria may be detected and/or measured as a health indicator, such as *Bifidobacteria* and *Lactobacillus* strains.

The target analytes that the biosensors of the present invention are adapted to detect may also be proteins or antigens related to skin distress. Preferably, these analytes are detectable on or at the skin surface, preferably prior to the presentation of clinically observable skin irritation. These may include stress proteins such as cytokines, histamine, and other immune response factors including interleukins (such as IL-1α, IL-2, IL-3, IL-4, and IL-8) and interferons (including interferons a and g). Again, these are preferably detectable by the biosensor 60 prior to the onset of clinically observable redness,

irritation, or dermatitis. Additionally, the biosensors of the present invention may be adapted to detect enzymes, or other biological factors, implicated in skin irritation (e.g., absorbent article dermatitis), including tryspin, chymotrypsin, and lipase.

In certain preferred embodiments of the present invention, the article may comprise a diagnostic panel. A "diagnostic panel", as used herein, comprises the combination of two or more biosensors, or other types of indicators, adapted to detect the presence of at least two of a specific group of substances. These substances can be indicators of the physical conditions or state of well being of a user, or the cause of a particular disease state, such as diarrhea, vaginal infections, sexually transmitted diseases ("STD's"), and other diseases. The biosensors can, for example, be adapted to detect the presence of at least two of a specific group of pathogens for the purpose of determining the class of pathogens or specific pathogen(s) causing a particular disease state, generally in order to provide a diagnosis leading to a specific course of remedial medical treatment. For example, the article may comprise a diagnostic panel adapted to determine the pathogenic cause, or causes, of diarrhea or vaginal infections. Examples of physical conditions or the state of well being that the diagnostic panel can be adapted to detect include, but are not limited to ovulation and the onset of menstruation. Examples of substances that the diagnostic panel can be adapted to detect in order to determine the onset of menstruation include, but are not limited to: progesterone, pH, and red blood cells (hemoglobin).

Alternatively, the article may comprise a diagnostic panel adapted to detect any of the potential bacterial causes of diarrhea or vaginal infections. In certain preferred embodiments, the diagnostic panel may comprise biosensors adapted to detect at least two of the following group of bacteria: EPEC, ETEC, EHEC, EAEC, EIEC, *Campylobacter jejuni*, *Vibrio cholerae*, and *Shigella* strains, including *S. sonnei* and *S. flexneri*. Preferably, the presence of any of the above bacterial causes of diarrhea or vaginal infections are indicated by the diagnostic panel. In any case, the signal to the user, caretaker, or health professional from the diagnostic panel preferably indicates the specific cause (i.e., bacterial pathogen) of the diarrhea or vaginal infections, allowing the early and specific treatment of the health condition.

Alternatively, the article may comprise a diagnostic panel adapted to detect any of the potential viral and bacterial causes of vaginal infections. In certain preferred embodiments, the diagnostic panel may comprise one or more biosensors adapted to detect at least one virus and one or more biosensors adapted to detect at least one bacteria. In any case, the signal to the user, caretaker, or health professional from the diagnostic panel preferably indicates the specific cause of vaginal infections, allowing the early and specific treatment of the health condition.

A non-limiting embodiment of an exemplary diagnostic panel 10 suitable for incorporation into a disposable absorbent article is shown in Figures 6B-6E. The diagnostic panel 10 includes two biosensors 12, a biosensor 14 adapted to detect *E. coli* H0157 and a biosensor 16 adapted to detect rotavirus. The diagnostic panel 10 may be made by obtaining biosensors 12 from the hereinbefore mentioned *Immuno*Card®STAT! *E. coli* 0157 Plus and *Immuno*Card®STAT! Rotavirus kits, available from Meridian Diagnostics. The biosensors are removed from their respective "cards" and attached to an exposed surface of a substrate 18 via any attachment or bonding means as known in the art, such as an adhesive. The substrate 18 is preferably a stiff cardboard material, although it may comprise any substrate such as paper, cardboard, a polyolefinic film, etc. As shown in Figure 6C, a mask 20 having openings corresponding to the biosensors 12 may be applied to the surface of the substrate 18 to ensure fluid/waste contact only with the biosensors 12 themselves and not the remainder of the substrate 18 surface. The substrate 18, or mask 20, may be made of any material such as plastic, cardboard, or paper, and may comprise markings, instructions, or other indicia to aid in performance of the test or the interpretation of the results. For example, the substrate 18 may comprise a color change "key" to assist the user in the correct interpretation of the results. The diagnostic panel 10 is attached to the wearing-facing surface of the absorbent article topsheet in the crotch region of the absorbent article corresponding to the location of a female wearer's pudendal region via any attachment or bonding means as known in the art, such as an adhesive. Alternatively, the diagnostic panel may be made by attaching the hereinbefore mentioned *E. coli* 0157 Plus and *Immuno*Card®STAT! Rotavirus biosensors directly to the wearing-facing surface of the absorbent article topsheet in the

region of the absorbent article corresponding to the location of a female wearer's pudendal region.

In any of the above embodiments, the absorbent article topsheet may comprise at least one aperture and the diagnostic panel 15 may be attached to the region of the underlying absorbent core corresponding to the topsheet aperture(s). The fluid/waste sample may optionally be diluted with a diluent, such as the diluent provided with the *Immuno*Card®STAT! Kit, upon removal of the absorbent article from the wearer or application of the fluid/waste sample to the biosensors 12. In any event, the results from the biosensors 12 may be read approximately 10 minutes after insult by a female wearer's fluids or waste or, if diluent was added, 10 minutes after the sample dilution.

The biosensors of the present invention may also comprise bio-recognition systems, including enzymes or binding proteins such as antibodies immobilized onto the surface of physico-chemical transducers. For example, a specific strain of bacteria may be detected via biosensors employing antibodies raised against that bacterial strain. Alternatively, a target bacteria may be detected by a bio-recognition element (including antibodies and synthetic or natural molecular receptors) specific to extracellular products of the target bacteria, such as toxins produced by that strain (e.g., *E. coli*). Exemplary enzyme electrodes that may be used to detect phenols (e.g. in urine) include tyrosinase based electrodes or polyphenol oxidase enzyme electrodes described in U.S. Patent No. 5,676,820 entitled "Remote Electrochemical Sensor," issued to Joseph Wang et al. on October 14, 1997 and U.S. Patent No. 5,091,299 entitled "An Enzyme Electrode For Use In Organic Solvents," issued to Anthony P. F. Turner et al. on February 25, 1992, respectively. Both of these patents are incorporated by reference herein.

In any of the foregoing examples, the specific microorganism may be directly detected or may be detected by binding a toxin, enzyme, or other protein produced by the organism or an antibody, such as a monoclonal antibody, specific to the organism. Exemplary biosensors adapted to detect proteolytic enzymes described in U.S. Patent No. 5,607,567 and toxins in U.S. Patent Nos. 5,496,452; 5,521,101; and 5,567,301.

In a non-limiting embodiment of an exemplary diagnostic panel for vaginal infections, the biosensor may be adapted to detect various specific types of bacteria that may be the cause of bacterial vaginosis, including *Gardnerella vaginalis*, *Prevotella bivia*, *Bacteroides* species, *Mycoplasma hominis*, *Mobiluncus* species. The biosensor may be adapted to detect non-specific types of bacteria that may be the cause of bacterial vaginosis. The biosensor may also be adapted to detect fungi such as *Candida* species, which is the cause of yeast vaginitis (or yeast infections). The biosensor may also be adapted to detect protozoa such as *Trichomonas vaginalis*, which is the cause of Trichomoniasis, a non-reportable sexually transmitted disease, Chlamydia, or other sexually-transmitted diseases. A non-limiting example of a commercially available biosensors adapted to detect *G. vaginalis* is the FEM EXAM® *G. vaginalis* PIP Activity TestCard available from Litmus Concepts, Inc. of Santa Clara, CA. The FEM EXAM® *G. vaginalis* TestCard is described in U.S. Patent No. 5,571,684. A non-limiting example of a commercially available biosensors adapted to detect non-specific causes of bacterial vaginosis is the FEM EXAM® pH and Amines TestCard available from Litmus Concepts, Inc. The FEM EXAM® pH and Amines TestCard is described in U.S. Patent No. 5,660,790. Other Litmus Concepts patents and patent publications of interest include: 5,268,146; 5,416,003; 5,585,273; 5,897,834; and PCT Publication WO 94/24306. Non-limiting examples of biosensor adapted to detect Candida and Chlamydia are described in U.S. Patent Nos. 5,741,662 and 5,773,234, respectively, issued to Quidel Corporation of San Diego, CA.

In other preferred embodiments, the diagnostic panel may comprise biosensors adapted to detect at least two of the following group of bacteria: various types of bacteria that may be the cause of bacterial vaginosis, including *Gardnerella vaginalis*, *Prevotella bivia*, *Bacteroides* species, *Mycoplasma hominis*, *Mobiluncus* species.

Fig. 1 shows a non-limiting panty liner embodiment 920 containing an exemplary diagnostic panel 960 for detecting the various causes of vaginitis. The diagnostic panel 960 shown in Fig. 1 contains five sensor elements, 962, 964, 966, 968, and 970. Each of these sensor elements is adapted to detect one or more of the causes of vaginitis alone, or in combination with one or more of the other sensor elements. Sensor element 962 is

adapted to detect pH. Sensor element 964 is adapted to detect the presence of amines. Sensor element 966 is adapted to detect *G. vaginalis*. Sensor element 968 is adapted to detect *Candida* species. Sensor element 970 is adapted to detect *Trichomonas vaginalis*.

The combination of sensor elements 962 and 964 can be used to detect non-specific causes of bacterial vaginosis. An early study of bacterial vaginosis (BV) involved comparisons of the pH of vaginal fluids of women known to be suffering from BV with those known to be free of the disease - Gardner, H.L., et al., *Am. J. Obstet. Gynecol.* 69: 962 (1955). All of the BV positive women in the study were determined to have a vaginal fluid pH greater than 4.5, and 91% of these women had a vaginal fluid pH greater than 5.0. Studies subsequent have now adjusted the pH threshold to 4.7.

The whiff test, which is one of the Amsel criteria, originated in a study by Pheifer, et al., *N. Engl. J. Med.* 298: 1429-1434 (1978), that reported the presence of a characteristic fishy amine odor upon the addition of 10% KOH to a vaginal fluid specimen from a woman with BV. The odor is caused by the alkaline volatilization of amine salts found in the vaginal fluid of women with BV.

An example is a test device for analyzing an aqueous liquid sample (usually a biological specimen) for a pH equal to or greater than a critical point in the range of 4.6 to 4.8 (preferably about 4.7) by a detectable transition.

A further example is a test device for detecting salts of volatile amines in an aqueous liquid sample (again, usually a biological specimen). This device contains a dry, solid gaseous amine-releasing substance in addition to an amine indicator retained in a matrix that is impermeable to aqueous liquids.

Preferred pH indicators are bromophenol blue, bromochlorophenol blue, bromocresol green, bromocresol purple, bromothymol blue, brilliant yellow, and nitrazine yellow. A particularly preferred pH indicator is nitrazine yellow which, when in combination with quaternary ammonium groups, changes directly from greenish-yellow to blue over a narrow pH range of approximately 0.1 pH units as the pH rises, the transition centering around pH 4.7.

The quaternary ammonium groups can be any groups capable of asserting a positive charge sufficient to form an ionic attraction with the negatively charged group(s) in the indicator. Preferred quaternary ammonium groups are lower alkyl ammonium groups in which the alkyl groups are C_1 - C_4 alkyl groups. Trimethylammonium groups are particularly preferred.

The amine test differentiates between amines volatilized by alkali and those that are not volatilized by alkali by incorporating solid alkali accessible to the specimen, an indicator accessible to a liquid specimen, and an indicator accessible only to vapors emitted by the specimen, in the same device. Thus, the specimen is first contacted with the solid alkali, then applied to both indicators, one of which sill undergo a color change regardless of the presence or absence of volatile amines, and the other a color change only in the presence of volatile amines.

The choice of solid alkali for the gas-releasing lamina is not critical and can vary. In general, alkali and alkaline earth metal aluminates, carbonates and hydroxides can be used. Best results will most often be achieved with the use of either sodium aluminate, sodium carbonate, or magnesium hydroxide. Sodium aluminate is particularly preferred.

Any indicator that changes color upon exposure to amines, and preferably amines in a fluid specimen that would otherwise be acidic, may be used. Bromocresol green is one example, and may be used here as well as in the pH test. Other examples are bromophenol blue, bromocresol purple, bromochlorophenol blue, nitrazine yellow, and various other indicators.

Sensor elements 962 and 964 can comprise the hereinbefore mentioned FEM EXAM® pH and Amines TestCard sensors available from Litmus Concepts, Inc. to detect non-specific causes of bacterial vaginosis.

Sensor element 966 is adapted to detect *G. vaginalis*. In 1988, a report by Thomason, et al. (*Obstet. Gynecol.*,71(4): 607 (1988)) suggested that bacterial enzyme activity, specifically proline iminopeptidase activity, in vaginal fluid may be a suitable marker for BV.

The assay is performed by contacting the sample with a solid-phase conjugate which is susceptible to cleavage by the hydrolase, and either during or subsequent thereto, contacting the sample with an indicator which undergoes a detectable change upon the action of a reporter group which is a portion of the conjugate and is liberated from it either partly or entirely by the action of the hydrolase.

The term "conjugate" is used herein to refer to a reporter group coupled to a substrate residue yet capable of cleavage or decoupling therefrom upon contact with the catalytically active hydrolase whose presence is being detected. The term "reporter group" or (interchangeably) "marker group" is used herein to refer to a moiety which can be hydrolytically released from the substrate residue by a hydrolase and which, in its free form, can react with an indicator to produce a detectable change. Such reporter groups include, but are not limited to, the following: phenols, naphthols, aromatic amines, amino acids, their derivatives and analogs. In a particularly preferred embodiment, naphthylamine, its derivatives or analogs are used as the reporter group.

If the hydrolase of interest hydrolyzes the conjugate at any other point other than freeing the reporter group, the hydrolase by itself would be incapable of releasing the reporter group in active form. One or more assisting hydrolases which could only act in conjunction with the hydrolase of interest could then be incorporated into the assay to complete the release of the reporter group in active form. The assisting hydrolase or hydrolases must therefore be ones which are incapable of releasing the reporter group directly from the intact conjugate, but instead capable of releasing the reporter group only from the cleavage product generated by the hydrolase of interest.

First, the hydrolase of interest, unable to release the reporter group directly, specifically hydrolyzes one or more bonds in the conjugate, thereby releasing a molecular fragment containing the inactive reporter group. Next, the assisting hydrolase (or hydrolases) releases the reporter group by hydrolyzing the bond between the substrate residue fragment and the reporter group in one or more steps. The net effect of the foregoing reaction sequence is the release of the reporter group only when the hydrolase of interest is present in the sample.

To illustrate an implementation of the present invention for detecting proline iminopeptidase activity, the sample is placed in a device which contains first and second solid supports, the first solid support being a Mylar® polyethylene laminate on which an L-prolyl-beta-naphthylamide, L-prolyl-beta-methoxynaphthylamide of hydroxy-L-prolyl-beta-naphthylamide conjugate is deposited, the second solid support being a Mylar® polyethylene laminate on which Fast Garnet GBC, a chromogenic indicator which undergoes a detectable change upon action of beta-naphthylamine, is deposited. The sample is placed in the device in such a manner that the sample contacts the first and second solid supports such that any beta-naphthylamine released by proline iminopeptidase activity in the sample is permitted to diffuse through the sample to the second solid support. The Fast Garnet GBC is then observed for a detectable change as an indication of the presence of the enzyme in the sample. The conjugate may be incorporated in a matrix of water-soluble polymer such as hydroxypropyl cellulose. The Fast Garnet GBC indicator may be incorporated in a water-insoluble matrix of ethylcellulose which contains a penetrant such as manganese chloride.

Sensor element 966 can comprise the hereinbefore mentioned FEM EXAM® *G. vaginalis* PIP Activity TestCard available from Litmus Concepts, Inc.

Sensor element 968 is adapted to detect *Candida* species. It has been discovered that enzymatically active *Candida albicans* aspartic protease is present in the vaginal fluid of women with vulvovaginal candidiasis. It has further been discovered that the presence of enzymatically active aspartic protease in a sample or specimen can serve as a marker for the detection and diagnosis of candidiasis. Accordingly, a method has now been developed for detecting candidiasis by assaying for the presence of enzymatically active aspartic protease in a sample.

In this method, a sample, e.g., vaginal fluid, is contacted with a solid support. The solid support with which the sample is contacted has a reporter enzyme (i.e., a signal generating enzyme) immobilized thereon. The reporter enzyme is immobilized on the solid support in a manner such that it is released from the solid support upon action of the enzymatically active aspartic protease if the enzymatically active aspartic protease is, in

fact, present in the sample. The sample after having been contacted with the solid support is combined with an indicator. The indicator is any chemical species which is susceptible to a visible or detectable change (such as, for example, a change in color) upon action of the reporter enzyme. If after contact with the sample the indicator undergoes a detectable change, enzymatically active aspartic protease is present in the sample and, hence, it can be said that candidiasis is present.

The term "reporter enzyme" or (interchangeably) "marker enzyme" is used herein to refer to a signal generating enzyme, i.e., an enzyme whose activity brings about a detectable change. Such reporter enzymes include, but are not limited to, the following: peroxidases, phosphatases, oxidoreductases, dehydrogenases, transferases, isomerases, kinases, reductases, deaminases, catalases, urease, and glucuronidase.

Presently preferred reporter enzymes are the peroxidases, such as, for example, horseradish peroxidase.

The reporter enzyme is immobilized on a solid support, i.e., an insoluble polymeric material, inorganic or organic matrix, gel, aggregate, precipitate or resin, in such a manner whereby the reporter enzyme is released upon action of the hydrolase whose presence is being assayed. Preferred solid supports in accordance with the present invention include, but are not limited to, the following: cellulose, agarose, dextran, polyacrylate, polyacrylamide, or their derivatives, chitin, sepharose, oxirane acrylic beads and polymeric dialdehyde, starch, collagen, keratin, elastin, bovine hide powder, bacterial cell wall peptidoglycan or fragments thereof, nylon, polyethylene terephthalates, polycarbonates, and controlled pore glass. Immobilization of the reporter enzyme on the solid support is carded out using conventional methods and procedures known to and understood by those skilled in the art.

The term "indicator" is used herein to refer to any chemical species which undergoes a detectable change as a result of the reaction or as a result of the culmination of reactions occurring when the enzymatically active hydrolase is present in the sample or specimen. The resulting detectable change is an indication that the enzymatically active hydrolase is present in the sample or specimen.

Preferred indicators are visual indicators and, in particular, chromogenic indicators, i.e., those in which the visible change is a change in color, including the

formation of color in an otherwise colorless material, upon action of the reporter or marker enzyme when it is released from the solid support by the enzymatically active hydrolase whose presence is being detected. Alternatively, the reporter enzyme may be capable of catalyzing the formation of a fluorescent signal, a phosphorescent signal, a bioluminescent signal, a chemiluminescent signal, or an electrochemical signal upon its release from the solid support by the action of the hydrolase. Additionally, the reporter enzyme may be capable of producing other visible or detectable signals, such as, for example, a clot, an agglutination, a precipitation, or a clearing zone.

A wide variety of chromogenic indicators (i.e., chromogens) and other species having a similar effect may be used as visual indicators with horseradish peroxidase as the reporter enzyme. Preferred chromogenic indicators in accordance with the present invention comprise a hydroperoxide and a chromogen including, but not limited to, one of the following: guaiac, 2-2'-azino-bis(3-ethyl-benthiazoline-6-sulfonic acid), tetramethylbenzidine, phenol, 4-aminoantipyrine, and 4, 5-dihydroxynaphthatlene-2, 7-disulfonic acid. A particularly preferred chromogenic indicator is comprised of a hydroperoxide and guaiac, a chromogen which is colorless in its reduced state and deep blue in its oxidized state.

Sensor element 970 is adapted to detect *Trichomonas vaginalis*. In yet another aspect of the present invention, a method is provided for detecting *Trichomonas vaginalis* by assaying for the presence of enzymatically active thiol protease in a sample, this method comprising: (a) contacting the sample with a solid support, the solid support having a reporter enzyme immobilized thereon in such a manner whereby the reporter enzyme is released upon action of the enzymatically active thiol protease; (b) combining the sample after having been contacted with the solid support with an indicator, the indicator being one which is susceptible to a detectable change upon action of the reporter enzyme; and (c) observing whether the indicator undergoes a detectable change, the detectable change being an indication of the presence of enzymatically active thiol protease in the sample and thus, *Trichomonas vaginalis*.

The panty liner 920 shown in Fig. 9 comprises a hybrid topsheet as described in U.S. Patent No. 6,004,893, Van Tilburg. The sensor elements can be attached to the wearing-facing surface of the panty liner topsheet 924. The sensors can be attached in the

region of the panty liner corresponding to the location of the wearer's vagina. The sensors can be attached via any attachment or bonding means as known in the art, such as an adhesive. Alternatively, the topsheet may comprise at least one aperture and the sensors may be attached to the region of the underlying absorbent core corresponding to the topsheet aperture(s).

The sensor elements may be in the nature of a plus or minus sign to indicate the presence or absence of the test analytes in a quantity above a certain threshold as shown in Figs. 1 and 1A. Alternatively, they may be adapted to provide a colorimetric indication of the quantity of test analytes as shown in Fig. 3, and the darkness of the color on the sensor elements can be compared with a comparison chart, such as that shown in Fig. 4, which indicates the level of test analytes present. The comparison chart can be provided in a number of suitable formats, including, but not limited to, in the form of a card that is packaged with the article on which the sensors are located, or on the outside of the package.

The sensor elements can be covered by a covering to prevent the test reagents in the sensors from coming in contact with the wearer's body, if test reagents are present. Preferably, the covering is clear and also flexible, so that it will not interfere with wearing the article, if the article is of a type to be worn adjacent to a wearer's body. The covering can be made of any suitable material, such as plastic, SARAN® wrap, MYLAR®, or the like. The covering can be apertured to allow body fluids to come into contact with the sensors, or it may be unapertured.

If a covering is used, it may be desirable to provide a fluid transport element, such as a wicking strip, underneath and/or on the sides of the sensors to bring the bodily fluids of interest into contact with the sensors.

Fig. 2 shows a non-limiting sanitary napkin embodiment 1220 containing an exemplary diagnostic panel 1260.

Figs. 7-9 show a non-limiting interlabial device embodiment 1320 containing an exemplary diagnostic panel 1360. Fig. 10 shows how the interlabial device 1320 may be held by a user for insertion into the space between the wearer's labia. Fig. 11 shows the interlabial device in place relative to the wearer's body.

Fig. 5 shows a non-limiting tampon embodiment 1620 containing an exemplary diagnostic panel 1660.

The biosensor used in the present invention may comprise one or more "proactive sensors". This is especially useful in embodiments where the detection of the target biologically reactive analyte precedes the onset of clinically observable health symptoms. As used in this application, the term "proactive sensor" refers to a sensor that is capable of detecting changes or signals on the body of the wearer (i.e., skin) or in the waste, i.e., inputs, that directly relate or, at a minimum, correlate to the occurrence of an impending or potential health or skin related even. Proactive sensors may respond to one or more specific inputs as described above.

A proactive sensor may detect an impending event or detect a parameter that directly relates, or at a minimum correlates to the occurrence of an impending event, particularly a systemic or skin health event or condition (i.e., the presentation of clinically observable indications or symptoms). An impending event that may be detected or predicted by a proactive sensor of the present invention may include diarrheal disease, skin irritation or rash (including candidiasis), and/or other types of illness or medical conditions of the wearer such as a parasitic infestation. The detected biological analyte may be one or more steps removed from the actual presentation of clinical symptoms. For example, the biosensor may detect potential precursors to the above conditions (e.g., fecal contamination of the skin that may precede the elicitation of stress proteins which may, in turn, precede clinically observable skin irritation. A parameter that correlates to an event is any measurable input, signal such as one or more of the potential inputs listed above, that correlates with the occurrence of the event within the frame of reference of the system (i.e., a signal caused by the waste or the wearer). Proactive sensors in an article may measure one or more different inputs in order to predict an event. For example, the proactive sensor may monitor for *Candida albicans* in the feces and residual colonic

bacteria on the skin (i.e., detecting residual contamination) both of which are signals that may precede skin irritation.

In biosensor embodiments wherein the bio-recognition element does not produce an easily visible signal (e.g., a color change), the biosensor may include a transducer in communication with the bio-recognition element in order to convert the physico chemical signal from the bio-recognition element into a usable signal to the wearer, caretaker, or component of the article (e.g., and actuator). Exemplary transducers may include electrochemical transducers (including potentiometric, amperometric, and conductimetric transducers), optical transducers (including flourescence, bioluminesence, total internal reflective resonance, and surface plasmon resonance), thermal transducers, and acoustic transducers, as known in the art. A power source, such as a miniature 3 volt watch battery or printed thin film lithium battery, may be connected with the biosensor 60 to provide any required power.

The effectiveness of the biosensors of the present invention may be measured with the Response Factor Test described in the Test Method section below. The Response Factor describes the ratio of the response of the biosensor when exposed to fluid/waste test material compared to the response of the biosensor when exposed to physiological saline solution and is useful in assessing the sensitivity of the biosensor for biologically active analytes expected to be found. The biosensors of the present invention preferably have a response factor of at least 2, 3, or 5, more preferably at least 10, and even more preferably at least 20.

If microorganisms are incorporated into a biosensor, they may be immobilized in the biosensor by techniques known in the art such as entrapment, adsorption, crosslinking, encapsulation, covalent attachment, any combination thereof, or the like. Further, the immobilization can be carried out on many different substrates such as known the art. In certain preferred embodiments, the immobilization substrate may be selected from the group of polymer based materials, hydrogels, tissues, nonwoven materials, woven materials.

In certain embodiments, the biosensor, including any biosensor embodiments, may comprise, be disposed on, or be operatively associated with a microchip, such as a silicon chip, MEMs (i.e., micro electromechanical system) device, or an integrated circuit.

Microchip-based biosensors may be known as "biochips". Regardless of the type of sensor, the microchip may comprise a multiplicity of sensor components having similar or different sensitivities, kinetics, and/or target analytes (i.e., markers) in an array adapted to detect differing levels or combinations of said analyte(s). Further, each biosensor in such an array may provide a different type of signal, including those types disclosed herein, and may be associated with different actuators and/or controllers. Also, each biosensor in an array may operate independently or in association with (e.g., in parallel, combination, or series) any number of other sensors in the array.

The biosensor may be disposed in and/or operatively connected to any portion of an absorbent article that will be exposed to the input that the biosensor is designed to detect. For the purposes of the present invention, the term "operatively connected" refers to a means of communication such that the biosensor may signal some portion of the article 10 when the biosensor detects an input. The biosensor may be separate from and operatively connected to another portion of the biosensor, another biosensor, an actuator, a controller or some other portion or component of the absorbent article 10. "Operatively connected" may, for example, include a means of communication such as an electrical connection via a conductive wire or member, via a transmitted signal such as radio frequency, infrared or another transmitted frequency communication. Alternatively, the biosensor may be operatively connected via a mechanical connection such as a pneumatic or a hydraulic connection.

The biosensor may be integral with the absorbent article 10, or may be installed by the caretaker or the wearer. The biosensor during the course of wearing the article, may also become at least partially detached from the article and may be adhered to the wearer's skin. The biosensor may be affixed, permanently or detachably (e.g., via a mechanical fastening system like Velcro™ or a water soluble adhesive) to a support structure, including adhesive tapes, cellulosic or synthetic webs, nonwoven highlofts, films, scrims, foams, and the like. Further, the biosensor may be completely contained within the absorbent article 10 or may have a receiving portion located in the absorbent article 10 such that it will come into contact with the desired input and another portion such as a transmitting portion located either in the article or outside the article. The biosensor may be external to the absorbent article 10 yet operatively connected to some

portion of the absorbent article 10 such that the biosensor may detect an input external to the absorbent article 10 and provide a signal to a controller and/or an actuator. In some embodiments, the biosensor may be separate from the article, e.g., separately applied to some portion of the wearer via adhesive or other means as known in the art, and/or may have one or more components separate from the article.

In some embodiments, a wiping means or element may be provided to allow the wearer or caretaker to clean sufficient bodily waste from the biosensor to allow a visual assessment or reading of the signal (especially for biosensor embodiments that provide such a signal). The wiping element may include a web (cellulosic or synthetic), nonwoven highloft, film, foam, rigid or semi-rigid squeegee like element, and the like disposed in the article and adapted such that the element may be used to clean the biosensor display. The wiping element may be at least partially affixed to an element (e.g., topsheet, backsheet, absorbent core) of the article, such as a topsheet, in proximity to the biosensor by any known means in the art. The wiping means may optionally comprise water or any other known cleaning aid to facilitate cleaning of the wearer or the biosensor display.

In certain preferred embodiments, the absorbent article 10 also may comprise an actuator. As used in this application, the term "actuator" refers to a device that comprises "potential" and a means of transforming that potential to perform or activate a "responsive function." The potential of the actuator may comprise either stored or potential energy or stored material. The actuator thus may perform or activate a responsive function by transforming potential energy to kinetic energy or by releasing or delivering a stored material. A "responsive function" is defined for the purposes of the present invention as a function performed upon the bodily waste, the wearer, the article, or a component or components thereof, or a signal to the wearer or the caretaker. A component of bodily waste may include, for example, moisture, electrolytes, enzymes, volatile gases, bacteria, blood, etc. A component of the wearer may also include skin, genitalia, the pudendal region, the anus, the anal sphincter muscle, etc. A component of the article may also include leg cuffs, waist cuffs or other waste barriers and/or containment components, side panels, ears, a chassis, an absorbent core, an acquisition component, a fastening system, the longitudinal or end edges, etc. Potential energy may be stored as mechanical,

electrical, chemical or thermal energy. "Kinetic energy" as used in this application refers to the capacity to do work or to perform a responsive function as described above (e.g., expansion of a compressed device, rotation of a twisted device, a gel that moves as it changes phases, coating or treatment of skin, inhibition of an enzyme, adjustment of pH, etc.).

The absorbent article 10 may also include a controller. A "controller" is defined for the purposes of this application as a device that receives an input from a biosensor and determines if one or more actions are to be taken. The controller may receive a signal from the biosensor and direct the actuator to perform a responsive function upon the bodily waste, the wearer, the article or a component thereof. Alternatively, the actuator may receive the signal directly from the biosensor and perform a responsive function upon the wearer, the waste, the article or a component thereof. The controller may include materials that undergo chemical or physical change, may be a chemical, mechanical or electrical device that processes information from a biosensor, etc. The controller may include a transducer comprising a polylayer Langmuir-Blodgett film, wherein one or more layers includes a bio-recognition element. Upon contact with water, Langmuir-Blodgett films are known to spontaneously reorganize, resulting in regions with more layers than the original film and other regions having fewer layers. This reorganization may expose the bio-recognition element to the environment preferentially in the presence of water, such as in bodily waste, which may contain the target biological analyte. Thus, the number of false positives can be reduced and the shelf-life of the biosensor can be extended. Alternatively, an electrical controller that receives signals such as electrical potential from an electrochemical biosensor may receive and monitor multiple electrical signals and may repeatedly trigger the actuator. The controller may be integral with the biosensor component, integral with the actuator component, or a separate component of the system.

The controller may be disposed in and/or operatively connected to any portion of a disposable article that will allow the controller to receive a signal from the biosensor and to provide a signal to the actuator. The controller may be integral with the absorbent article 10, or may be installed by the caretaker or the wearer. The controller may be completely contained within the article such as absorbent article 10, may have a portion

located in the article and a portion located outside the article, or may be located completely outside the absorbent article 10. The controller or a portion of a controller may be operatively connected to one or more biosensors, one or more actuators 90, another portion of the controller or another portion of the absorbent article 10. The controller, for example, may receive a signal from the biosensor and provide a signal to the actuator, e.g., by a radio frequency (rf) transmission.

Although distinct structural elements may perform the biosensor, actuator and controller functions, the biosensor, actuator and/or controller functions of the present invention need not be performed by distinct structural elements. The biosensor and controller functions, for example, may be performed by the same structural element.

A "responsive system" is defined for the purposes of this application as a system that includes a biosensor and an actuator that acts upon the bodily waste, the wearer, the article, or a component or components thereof when the biosensor detects the appropriate triggering input. Upon sensing a given input parameter, the actuator effects the release of stored energy or the release or delivery of stored material to perform a responsive function. For example, when a proactive biosensor including a transducer detects an impending event, the transducer provides a signal to the actuator effecting the release of stored energy. By detecting an input signal prior to the impending event, a responsive system in the article may be triggered to prepare for the event or to signal the caregiver or the wearer of the impending event. This allows construction of articles in which the waste-management or treating technology is initially "hidden" or unobtrusive, but which is available at, or just before, the moment of need and/or in which the article may provide the caregiver or the wearer the opportunity to prepare for an event in advance (e.g., administer a prohylactic treatment to the wearer in the event of detected pathogenic microorganisms). Regardless of the specific input, the biosensor in these embodiments may trigger an actuator to perform an action on the article, the wearer or the environment to prepare for the occurrence of the event or provide a signal to the caregiver that the impending event is about to occur. If the biosensor comprises a sensing system, one actuator may be triggered by different biosensors and/or signals, or different actuators may be triggered by different biosensors and/or signals. Alternatively, one biosensor and/or signal may trigger multiple actuators.

A responsive system may respond in either a "continuous" or a "discontinuous" manner. As used in this application, a "continuous responsive system" refers to a responsive system in which the output is quantitatively dependent upon the quantity of the input, i.e., continuously increasing quantities of the input are required to effect continuously increasing quantities of the output, or where the output of the responsive system comprises a passive release of a stored material. A super absorbent polymer placed in an absorbent core of an article, for example, provides a continuous response in which the output is quantitatively dependent upon the quantity of the input, i.e., as increasing quantities of liquid waste contact the super absorbent polymer, an increasing amount of the polymer contains that liquid until the capacity of the polymer is exhausted. A stoichiometric chemical reaction is another example of a system having a continuous response to increasing output. In the reaction A + excess B $\rightarrow$ C, for example, the amount of excess B converted to C is stoichiometrically and, therefore "continuously," related to the amount of A available in the system.

A "discontinuous responsive system" of the present invention, however, refers to a responsive system that has an output function that is essentially independent of the quantity of the input beyond a threshold level. For example, when one or more threshold levels of a given input are met, the responsive system may release all or a pre-designated portion of its stored energy or deliver, i.e., actively transport, all or a pre-designated portion of its stored material to perform a specific responsive function. In an ideal embodiment of the present invention, the output function, f(x), includes a "step" function as shown in Figure 3A. In this embodiment, the rate of change in the output with increasing levels of input (d(output)/d(input)), i.e., the slope or first derivative f'(x) of the output function f(x), is preferably essentially zero when the amount of input is above or below the threshold level. At the threshold level, however, the d(output)/ d(input) rate of change preferably approaches infinity. Thus, in the ideal discontinuous response, the limit of the function f(x-ε) as $\varepsilon \rightarrow 0$ is not equal to the limit of the function f(x+ε) as $\varepsilon \rightarrow 0$, i.e., $\lim_{\varepsilon \rightarrow 0} f(x-\varepsilon) \neq \lim_{\varepsilon \rightarrow 0} f(x+\varepsilon)$.

The present invention, however, recognizes that in the physical world an ideal instantaneous step change at the threshold level is not necessary and may not even be possible in many instances. In a preferred embodiment, it is only necessary that the output function have a virtual step change with very little change in the input at or around the threshold level of the input. Thus, the present invention contemplates a discontinuous responsive system of the present invention having an output function that responds in a sufficiently discontinuous manner in the transition region such that the output function has at least a minimum relative degree of steepness in the transition region. While not wishing to be limited to a particular method of describing or modeling a discontinuous system, in a preferred method of determining whether a given output function performs in a sufficiently discontinuous manner as defined for the purposes of the present invention, the slope of the output curve at the inflection point is compared with the relative slope of a line between the first and last points of the transition region. For example, Figure 4A shows a graph of an exemplary output function, f(x) along with aligned graphs of the first, f'(x), and second, f''(x), and third, f'''(x), derivatives of the exemplary output function. The output function f(x) describes the effect of the in put (x or I) on the output or response (R(I)). For purposes of the present invention, the transition region is defined as the region between the relative maxima, $R(I_1)$, and the minima, $R(I_2)$, of the second derivative, f''(x), of the output function, f(x). The relative maxima, $R(I_1)$, and the relative minima, $R(I_2)$, are points at which the third derivative, f'''(x), equals zero. The inflection point, I_0, is defined as the point in the transition region at which the second derivative, f''(x), equals zero, i.e.,

$$\left.\frac{d^2R}{dI^2}\right|_{I=I_0} = 0.$$

The comparison of the slope of the output function at the inflection point to the slope of a line between the first and the last points of the transition region can be described by the equation:

$$\left.\frac{dR}{dI}\right|_{I=I_0} = k\,\frac{(\Delta R_T)}{(\Delta I_T)}.$$

In this equation dR/dI at the inflection point is the first derivative of the output function at that point. The term ΔI_T is the change in the input to the responsive system between the first, I_1, and last, I_2, points of the transition region, i.e., $I_2 - I_1$, and the term ΔR_T is the change in the response of the output function between the first and last points of the transition region, i.e., $R(I_2) - R(I_1)$. The coefficient k is a proportional constant that describes the relative steepness of the slope of the output function at the inflection point, I_0, compared to the slope of a line between the first and last points of the transition region. In order that the responsive system have a discontinuous output function, the proportional constant k must be at least about 2.0, preferably at least about 3.0, more preferably at least about 5.0, even more preferably at least about 10.0, with at least about 100.0 being the most preferred.

In certain embodiments, the relative degree of steepness in the transition region of a discontinuous responsive system may also be modeled by a transfer function of a control system having a series of an integer number, n, first order lags with an equal time constant. The transfer function of the responsive system is defined for the purposes of the present invention as the ratio of the Laplace transforms of the output (responding variable) to the input (disturbing variable). See, e.g., Robert H. Perry & Don Green, Perry's Chemical Engineers' Handbook, Sixth Ed., Chap. 22 (McGraw Hill, Inc. 1984). As shown in Figure 12, the relative degree of steepness of an output function may be approximated by the formula: $KG(s) = K/(Ts + 1)^n$ in which KG(s) is the transfer function, K is a proportional element, T is the time constant of the system, and n is the integer number of first order time lags. In this model, as the number n increases, the steepness of the output function in the transition region increases, and the model begins to approximate a discontinuous responsive system. Certain discontinuous responsive systems of the present invention preferably may be modeled by the above formula when n is greater than or equal to about 25, with n being greater than or equal to about 50 being more preferred, and n being greater than or equal to about 100 being the most preferred.

As shown in Figure 13A, a responsive system of the present invention may include a single threshold level at which the responsive system may release all of its stored energy to perform a specific responsive function or may include multiple threshold levels at which the system may release a pre-designated portion of its stored energy to perform one or more specific responsive functions at each of the threshold levels. In an embodiment having a single threshold level, for example, the responsive system may release all of its stored energy to perform the entire responsive function when that threshold level is met. In such a single threshold embodiment, In this example, the discontinuous responsive system includes a system that has two states such as on or off. When a threshold quantity of an input such as a target biological material is present in the absorbent article, the responsive system may perform a single responsive function upon the waste, the wearer, the article or a component thereof, such as enveloping the waste away from the skin of the user or providing an easily detectable visual signal to the wearer or caregiver. Thus, the discontinuous responsive system may perform a one-time "switch-like" function that changes from one state to another in the presence of a threshold level of an input.

Alternatively, as shown in Figure 13B, the responsive system may have multiple threshold levels at which when each threshold level is met the system may release a given "quanta" of energy or deliver a given quantity of material to perform a specific responsive function. In this embodiment, when each threshold level is met, a portion of the entire responsive function may be performed and/or different independent responsive functions may be performed in response to different threshold levels being met. For example, a responsive system may monitor a target enzyme and when each threshold enzyme level is met may deliver an equal or unequal quantity of enzyme inhibitor(s) or lotion, or deliver a pH buffer at the first threshold level and perform another responsive function such as delivering a quantity of enzyme inhibitor(s) at the second threshold level. In each transition region, the responsive system responds essentially the same as the transition region in the single threshold embodiment described above.

In addition, a responsive system may monitor multiple inputs such as one or more pathogenic bacteria and/or one or more target enzymes and perform one or more responsive functions when the threshold levels of the different inputs are met or may perform one responsive function only when two or more of the threshold levels of the

different inputs are met. Thus, a controller may monitor multiple different inputs and perform a different responsive function when the threshold level of the different inputs are met. Alternatively, the controller may perform a logic OR-gate type function such that a responsive function may be performed when one or more threshold levels of the multiple inputs are met. The controller may also perform a logic AND-gate type function such that a responsive function may be performed when each threshold level of two or more different inputs is met.

The responsive system may also comprise a "closed loop" or an "open loop" system. A "closed loop" system, which is also referred to as a "feedback control loop" system, includes distinct biosensor and actuator components and performs a responsive function upon the input. In some preferred embodiments, the system may also use a detection or a measurement of an element or a parameter of the output condition as at least one trigger of the responsive function that is performed upon the input. The output condition may be the state of the input condition after the actuator has had the opportunity to perform a responsive function on the input condition. The responsive function may be performed when the output condition reaches a threshold level, or may be performed only when the output condition and one or more other conditions are met. Acting upon the input may include acting upon the element sensed, e.g., sensing a microorganism and acting upon the microorganism, or may include acting upon a composition of which the element sensed is an integral component. As described above, a feedback control loop system includes at least two distinct components: the biosensor 60 and the actuator. The biosensor detects an event, or a parameter associated with that event. The actuator receives a signal and performs a responsive function on the input condition detected by the biosensor. The feedback control loop may further include a controller. In this case, the biosensor may provide a signal to the controller, and the controller may direct the actuator to perform a responsive function upon the input condition. The controller may be a separate component of the responsive system or the controller function may be performed by the biosensor and/or the actuator.

The feedback control loop may be "non-modulating" or "modulating." In a "non-modulating" feedback control loop responsive system the responsive system acts as a one-time switch in which the actuator performs a responsive function on the input when the

threshold level of the output condition is met. For example, the biosensor may detect the presence of or measure the concentration of a specific pathogenic microorganism, and the actuator may signal the caretaker of a potential incipient infection. In this example, the actuator acts upon the input detected by the biosensor. A "modulating" feedback control loop, however, includes a biosensor, an actuator and a controller. In a modulating feedback control loop, the output condition is monitored constantly or repeatedly, and the controller directs the actuator to perform a responsive function on the input in order to maintain the output condition at a desired set point or within a desired range or to provide a continuous measurement of the level or concentration of the target biological analyte.

An "open loop" system, however, is a system that responds to the input to perform a responsive function without using feedback, i.e., the output has no effect upon the sensed input entering the system. An open loop system may include a responsive system that has a single device that performs the functions of both the biosensor and the actuator or may have distinct biosensor and actuator components in which the actuator acts upon something other than the input. A super absorbent polymer placed in an absorbent core of a disposable absorbent article, for example, provides an open loop response because the polymer only includes a single device that performs the functions of the biosensor and actuator. Alternatively, an open loop responsive system may include a biosensor that detects bodily waste or a component of that bodily waste, and an actuator that performs a responsive function in a continuous or a discontinuous manner on something other than the input detected by the biosensor.

The present invention includes responsive systems that provide a discontinuous or continuous response, whether open loop or closed loop. Other responsive systems are described in United States Patent Application Numbers 09/106,424 entitled "Disposable Article Having A Discontinuous Responsive System" filed on June 29, 1998 (P&G Case Number 7197); 09/107,563 entitled "Disposable Article Having A Responsive System Including A Feedback Control Loop" filed on June 29, 1998 (P&G Case Number 7198); and 09/106,225 entitled "Disposable Article Having A Responsive System Including A Mechanical Actuator" filed on June 29, 1998 (P&G Case Number 7199), each of which is incorporated herein by reference.

The disclosures of all patents, as well as any corresponding published foreign patent applications), and publications mentioned throughout this patent application are hereby incorporated by reference herein. It is expressly not admitted, however, that any of the documents incorporated by reference herein teach or disclose the present invention.

WHAT IS CLAIMED IS:

1. A multiple diagnostic device for a woman's health, comprising:

   a biosensor being able to detect multiple target analytes in a women's bodily fluids, wherein the analytes are germane to a women's health.

2. The multiple diagnostic device of Claim 1 wherein the biological analyte is germane to a woman's health indicating at least one of the following including 1) the onset of menstruation, 2) the presence of ovulation, 3) the presence of a sexually transmitted disease, 4) the state of pregnancy, 5) the presence of infection, 6) the presence of hormone fluctuations, 7) ovarian reserve, 8) the presence of menopause, 9) the presence of osteoporosis, 10) the presence of an iron deficiency, 11) electrolyte balance, 12) nutritional status, 13) stress level and 14) combinations thereof.

3. The multiple diagnostic device of Claim 1 wherein the biosensor comprises at least one bio-recognition element for use in detecting the at least one biological analyte.

4. An absorbent article, comprising:

   a topsheet;

   a backsheet joined to the topsheet;

   an absorbent core positioned between the topsheet and the backsheet; and

   a multiple diagnostic device being positioned about the absorbent article, the multiple diagnostic device being adapted to detect at least one target biological analyte in bodily fluids, wherein the biological analyte is germane to a woman's health.

5. The absorbent article of Claim 4 wherein the biological analyte is germane to a woman's health indicating at least one of the following including 1) the onset of menstruation, 2) the presence of ovulation, 3) the presence of a sexually transmitted disease, 4) the state of pregnancy, 5) the presence of infection, 6) the presence of hormone fluctuations, 7) ovarian reserve, 8) the presence of menopause, 9) the

presence of osteoporosis, 10) the presence of an iron deficiency, 11) electrolytc balance, 12) nutritional status, 13) stress level and 14) combinations thereof.

6. The absorbent article of Claim 4 wherein the multiple diagnostic device is a biosensor that comprises at least one bio-recognition element for use in detecting at least one biological analyte.

7. The absorbent article of Claim 6 wherein the absorbent article comprises at least one diagnostic panel having at least one biosensor, the biosensor being adapted to detect at least one target biological analyte in bodily fluids, wherein the biological analyte is germane to a woman's menstrual cycle.

8. The absorbent article of Claim 4 wherein the absorbent article is selected from the group consisting of a sanitary napkin, an interlabial device, a tampon, a patch, a liquid collection device and combinations thereof.

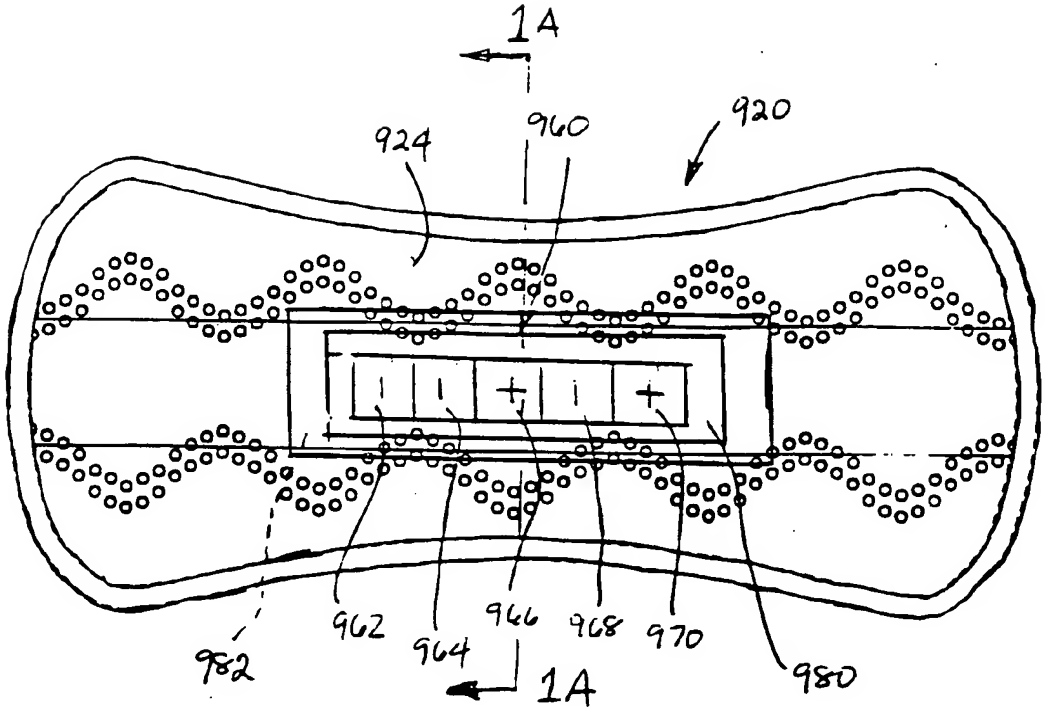

FIG.1

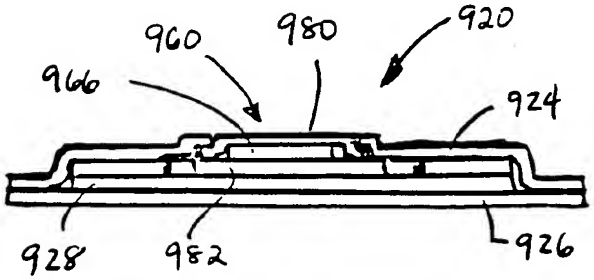

Fig. 1A

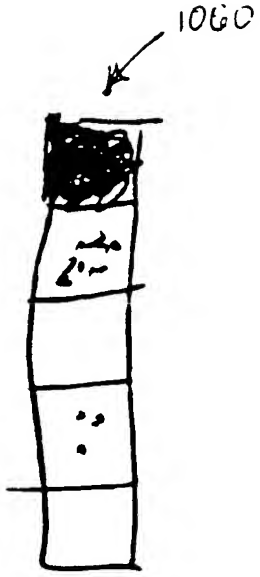

Fig. 3

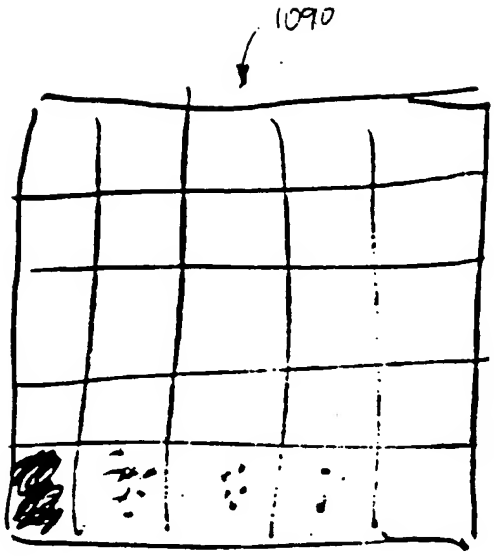

Fig. 4

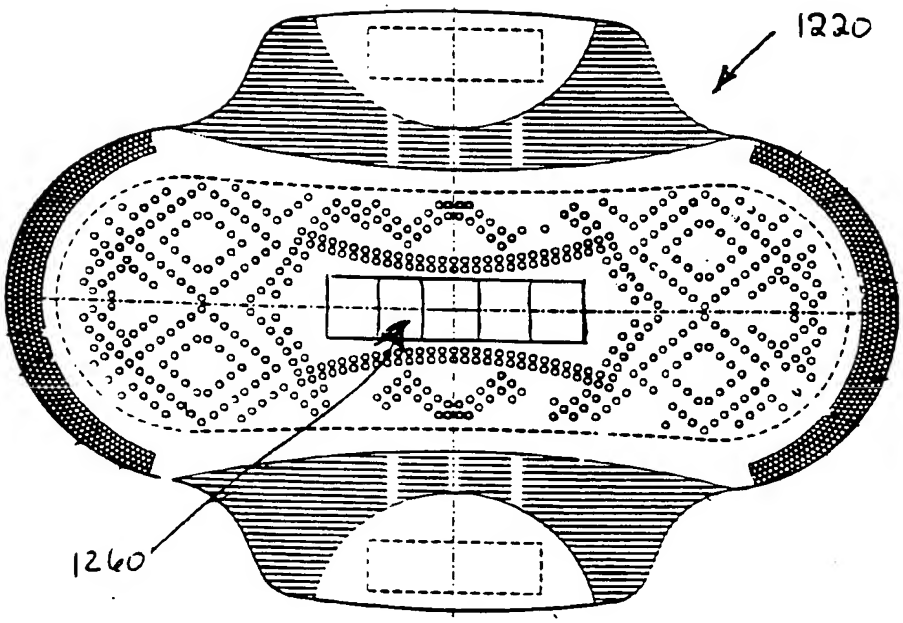

Fig 2

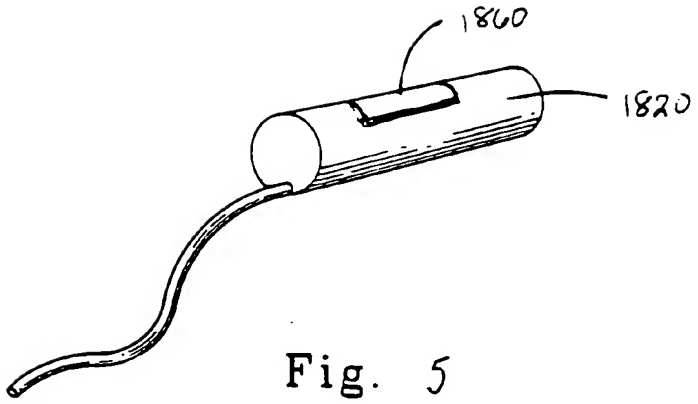

Fig. 5

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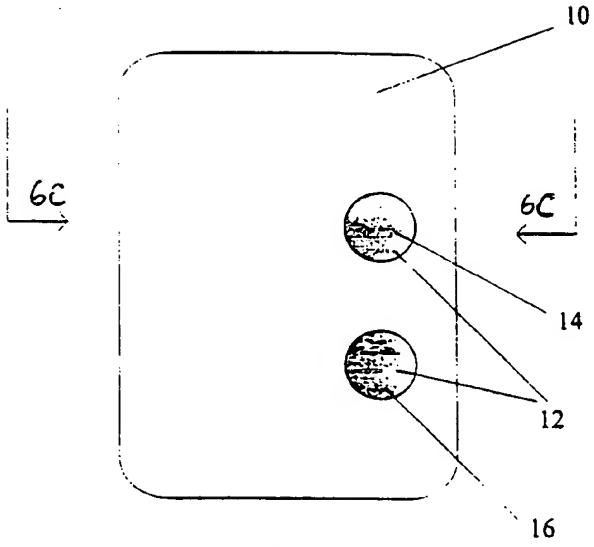

Figure 6B

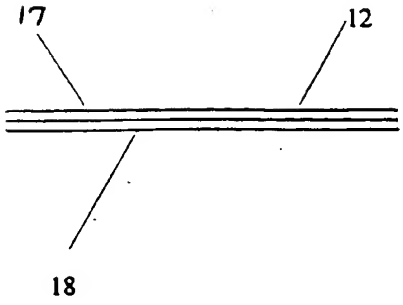

Figure 6C

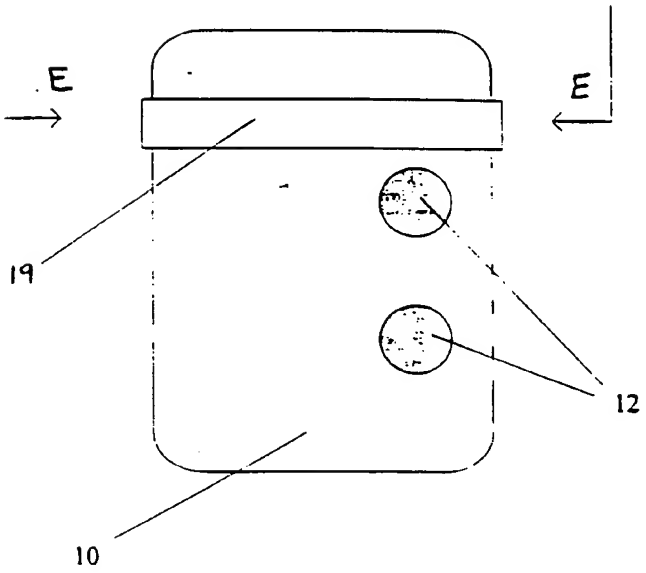

Figure 6D

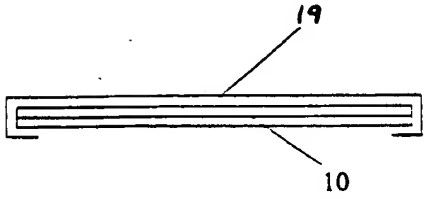

Figure 6E

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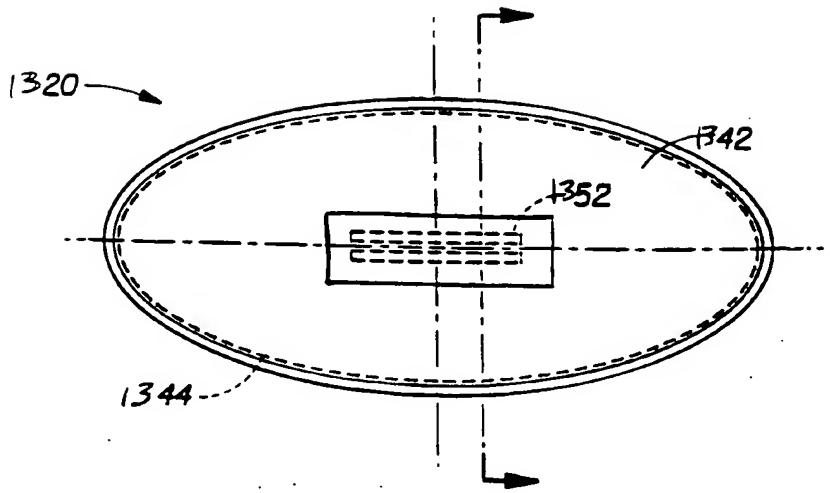

Fig. 7

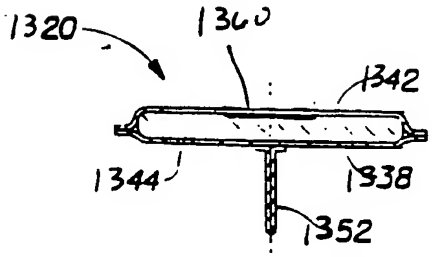

Fig. 8

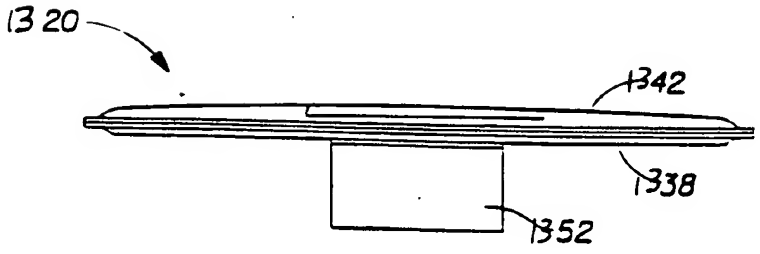

Fig. 9

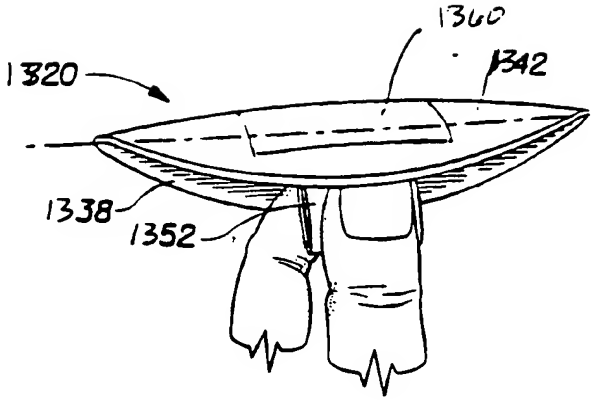

Fig. 10

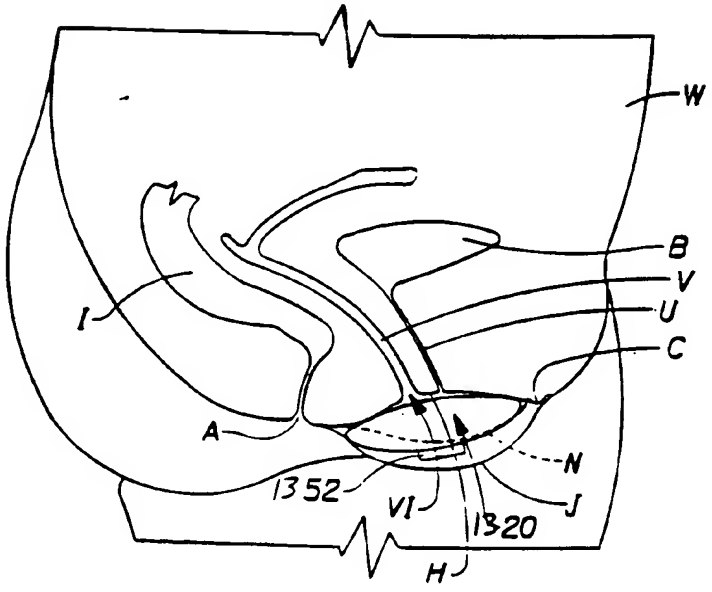

Fig. 11

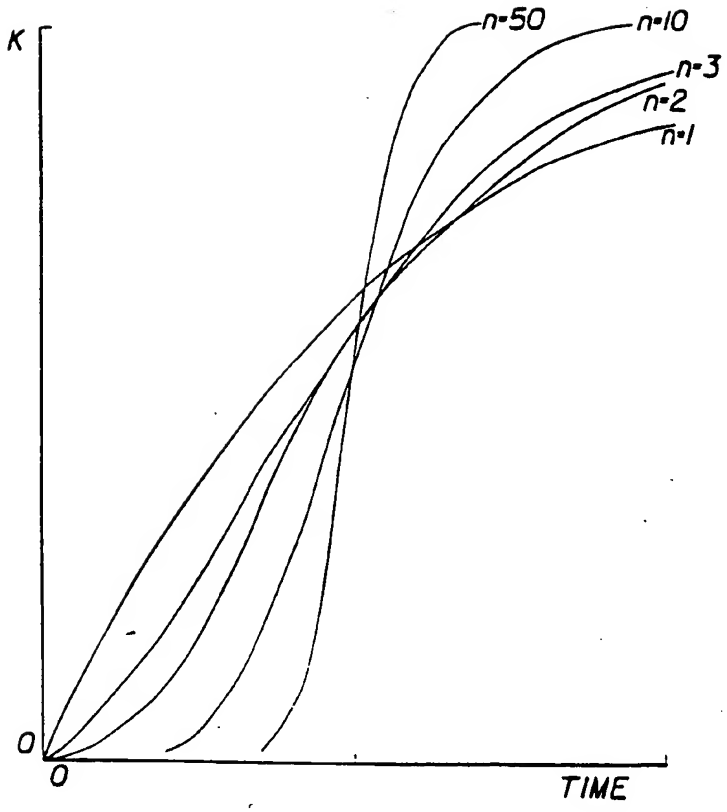

Fig. 12

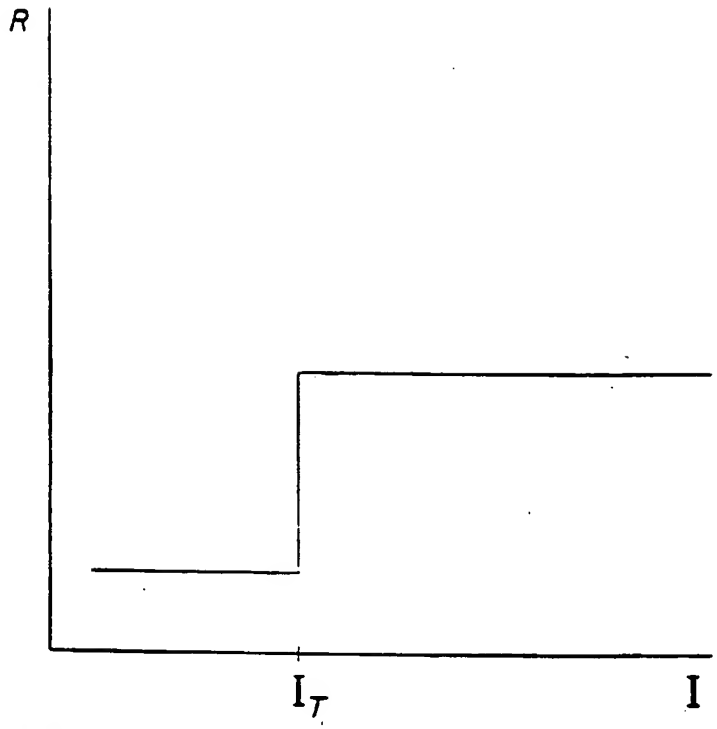

Fig.13A

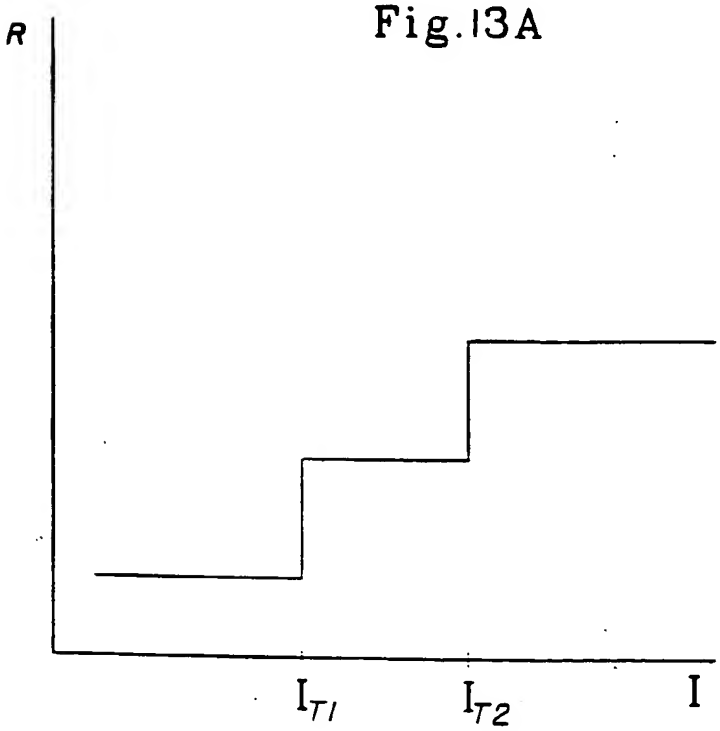

Fig.13B